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Recent molecular advances in essential hypertension

Alcohol and risk for hypertension

There is continued interest in the possible causal links between alcohol and blood pressure. Although a wealth of data, both anecdotal and systemically collected, supports a direct causal link, several confounding factors play a significant role, notably age, gender and lifestyle. Several genes are now known to influence alcohol metabolism and independently regulate blood pressure. Alcohol dehydrogenase 2 is recognised as playing a major role in the removal of acetaldehyde, the primary metabolite of alcohol which is produced in the liver. Some people have a genetic polymorphism that produces an unusually active enzyme leading to accumulation of excess amounts of acetaldehyde. These individuals, mainly from China and East-Asia, are unable to tolerate alcohol because the accumulated acetaldehyde makes them feel ill. There is good evidence that homozygotes exhibit far worse adverse reaction compared to heterozygotes, but both have lower thresholds to the untoward side-effects of alcohol consumption.

This subject has been the focus of a recent paper (PloSMed 5:e52, 2008, doi:10.1371) which examines the evidence collected from 10 cross-sectional Japanese studies that looked at phenotype-genotype correlations of alcohol dehydrogenase 2 and alcohol metabolism, and its causal links with increased blood pressure. This meta-analysis provides evidence that men with two wild copies of the allele are indeed able to consume far more alcohol than men with two mutated copies. Homozygotes were also more likely to be hypertensive (odds ratio 2.42, 95% CI 1.66–3.55) and had significantly higher diastolic and systolic blood pressure. Even heterozygotes, who were moderate drinkers, were 70% more likely to have hypertension than men homozygous for the mutated allele (odds ratio 1.72, 95%CI 1.17–2.52). This study supports the argument that genotype has an effect independent of lifestyle such as diet, excess salt intake, lack of exercise, and other confounding factors.

Researchers estimate that homozygotes carry a risk of increased blood pressure (0.16 mmHg for diastolic and 0.24 mm Hg for systolic blood pressure) with each extra gram of alcohol consumed. Thus, the authors inferred that both homozygotes and heterozygotes with the alcohol dehydrogenase 2 gene polymorphism are at increased risk of high diastolic and systolic blood pressure, in addition to the risks associated with lifestyle and several other confounding factors.

A possible genome-based vaccine for hypertension

Among the several genes that predispose to blood pressure, genes that regulate the rennin-angiotensin-aldosterone (RAA) pathway feature high on the list. Gene products of RAA include several endogenous peptides. Drugs that either inhibit the conversion of angiotensin converting enzyme I (ACEI) to ACEII (e.g., captopril, enalapril and ramipril, etc.) or interfere with the function of ACEII receptor (e.g., candesartan, losartan and valsartan) are prescribed to millions of hypertensive people world-wide. However, it not clearly known what proportion of people with essential hypertension actually has pathogenic mutations or polymorphisms within the ACE genes? The recent

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therapeutic attempt targeting ACE focuses on blocking the effect of the endogenous ACE II peptide by linking it to a virus-like particle (Lancet 371:821–827, 2008). This is perhaps the first report on a possible vaccine against high blood pressure. In a small preliminary trial, three injections of the vaccine over three months induced enough antibodies in mildly hypertensive volunteers to reduce daytime blood pressure by 9 mmHg/4 mmHg compared with placebo ($P = 0.015$ for systolic and $P = 0.064$ for diastolic blood pressure). The desired effect was best achieved with the highest dose, which also blunted the usual morning surge between 5 and 9 AM. Although no serious side effects were observed, almost 20% reported flu-like symptoms. Researchers argue that patients would only need injections a few times a year. A half-life of around 17 weeks is only achievable after a second round of injections. Little is known about the safety of this vaccine. Furthermore, what benefits will this therapeutic approach offer, given that there are several potent anti-hypertensive drugs are available on the market? Unlike drugs, vaccines are irreversible and thus cannot be stopped or altered when they cause side effects. Caution is also advised on the unwanted and unpredictable consequences of blocking the RAA system. Furthermore, immune stimulation could even cause auto-immune disease, although the authors of this interesting paper found no signs of this in their brief trial. Nevertheless this is a major advance in molecular biotechnology that could lead to development of new vaccines for the prevention and therapy of complex non-communicable diseases.

Personalized medicine: the emerging paradigm of warfarin

Among the few examples of personalized medicine, customised warfarin prescribing has now become an accepted practice. The US Food and Drug Administration approve genotyping for genetic variations in genes encoding for the two key enzymes metabolising warfarin. Although the P-450 enzyme CYP2C9 is the key enzyme involved in warfarin metabolism, the secondary enzyme, vitamin K epoxide reductase (VKORC1), should probably be the main tool in warfarin therapy. This has emerged in a recent study by Schwartz et al. (NEJM 358:999–1008, 2008) based on a cohort of 297 US adults. Genetic variations in VKORC1 were found to be more useful than CYP2C9 gene polymorphisms for predicting sensitivity to initial warfarin therapy.

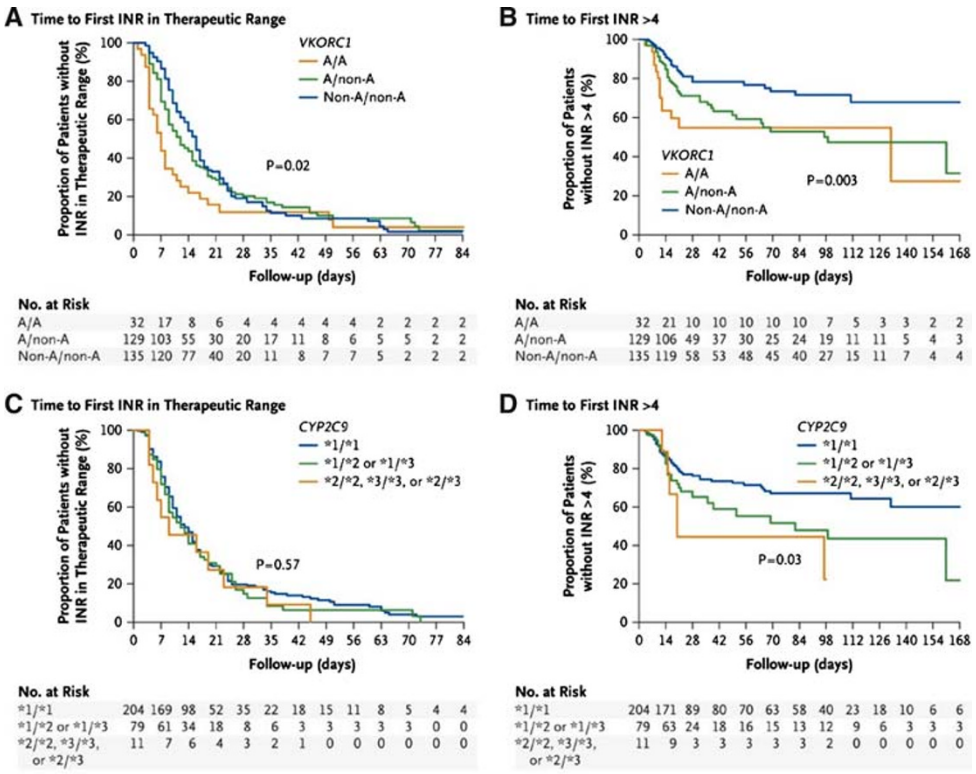

Fig. 1 Association between specific genetic variants and study outcomes. The graphs show the association between the time to the first international normalized ratio (INR) within the therapeutic range and the time to the first INR of more than 4 for patients carrying genetic variants for vitamin K epoxide reductase (*VKORC1*) (Panels **a** and **b**) and for cytochrome P-450 2C9 (*CYP2C9*) (Panels **c** and **d**). Adapted with permission from The New England Journal of Medicine (Schwartz et al. N Engl J Med 358(10):999–1008, 2008)

Homozygotes with the A VKORC1 haplotype had higher international normalised ratio (INR) values in the first week than the non-A homozygous patients. These individuals achieved higher INR more rapidly, and exceeded the target INR values (see Fig. 1). On the other hand, CYP2C9 genotyping did not help in predicting early sensitivity to warfarin. Warfarin dosage adjustments were only possible after week 2 of commencing the anti-coagulation regimen. However, neither of the genetic polymorphisms affected the patient's risk of bleeding.

The above report provides further evidence of the growth of genomic-based personalised medicine (NEJM 358:1061, 2008). Nevertheless, we have a long way to go before we are confident of this approach in pharmacotherapeutics. We need more information on the extent to which genetic polymorphisms influence warfarin sensitivity, supported by clinical trials to test whether treatment guided by genotyping is any safer and/or more effective than traditional strategies.